What Can We Learn from Genomically-Driven Trials in Other Tumors?

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Genomically-Driven Oncology Trials

Basket

Test the effect of targeted agents on same genomic alterations across a variety of cancer types

Umbrella

Test the effect of targeted agents on different genomic alterations in a single cancer type

Basket Trials

- Imatinib (B2225)
- Pharmaceutical Trials
- Institution Trials
- MPACT
- MATCH

Imatinib Study (B2225)

186 patients with **40** different refractory tumors and no available treatment

KIT, ABL, or PDGFR

Imatinib 400 or 800mg qday
Primary Endpoint ORR

	Others	DFSP	AS Mastocytosis	HES/CEL	MDS/MPD
ORR		10/12 (83%)	1/5 (20%)	4/14 (29%)	4/7 (57%)
Case Report ORR		5/6	7/7 FIP1L1-PDGFRα Fusion kinase	61/61 FIP1L1-PDGFRα Fusion kinase	13/16 PDGFR gene re-arrangement

Basket Trials

- Imatinib (B2225)
- Pharmaceutical Trials
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- MPACT
- MATCH

Industry Basket Trial Examples

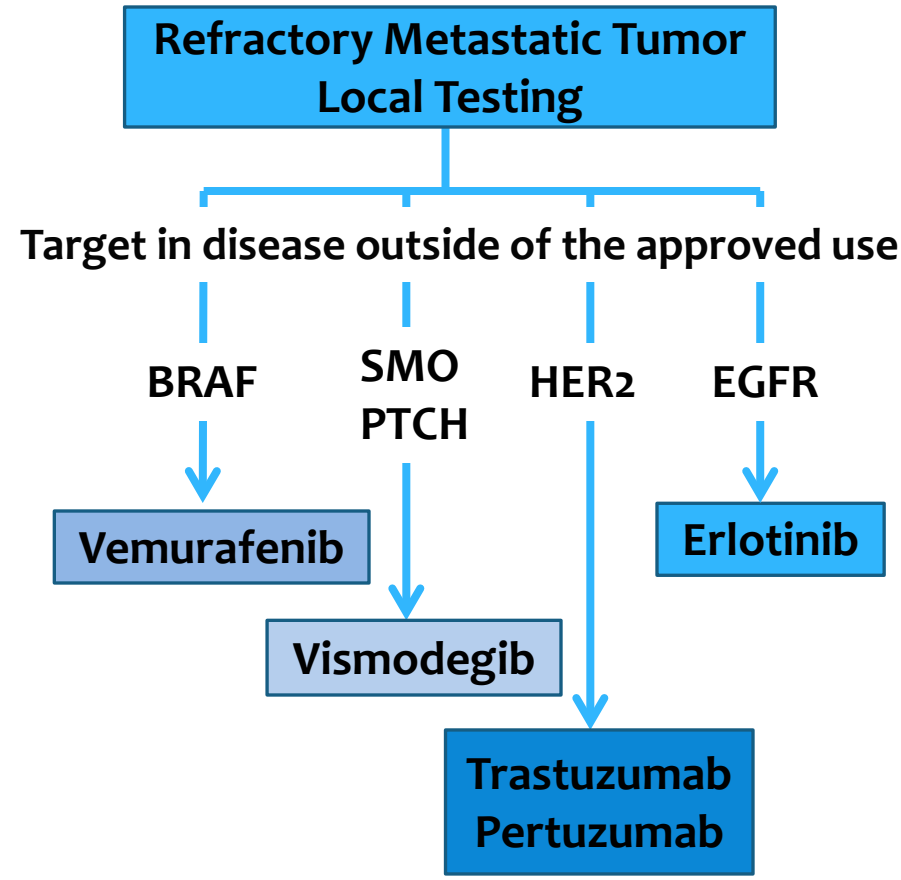
Signature

- Refractory metastatic tumor tissue sent for local testing
- Result identifies potential target Physician rapidly opens study site
- Eligible patient enrolls on targeted clinical trial:

- BKM120 (PanPI3Ki)
- TK1258 (FGFRi)
- MEK162 (MEKi)
- LGX818 (RAFi)
- LED225(SMOi)

- Agents Planned: LDK378 LEE011, BGJ398 and combinations

MyPathway



Basket Trials

- Imatinib (B2225)
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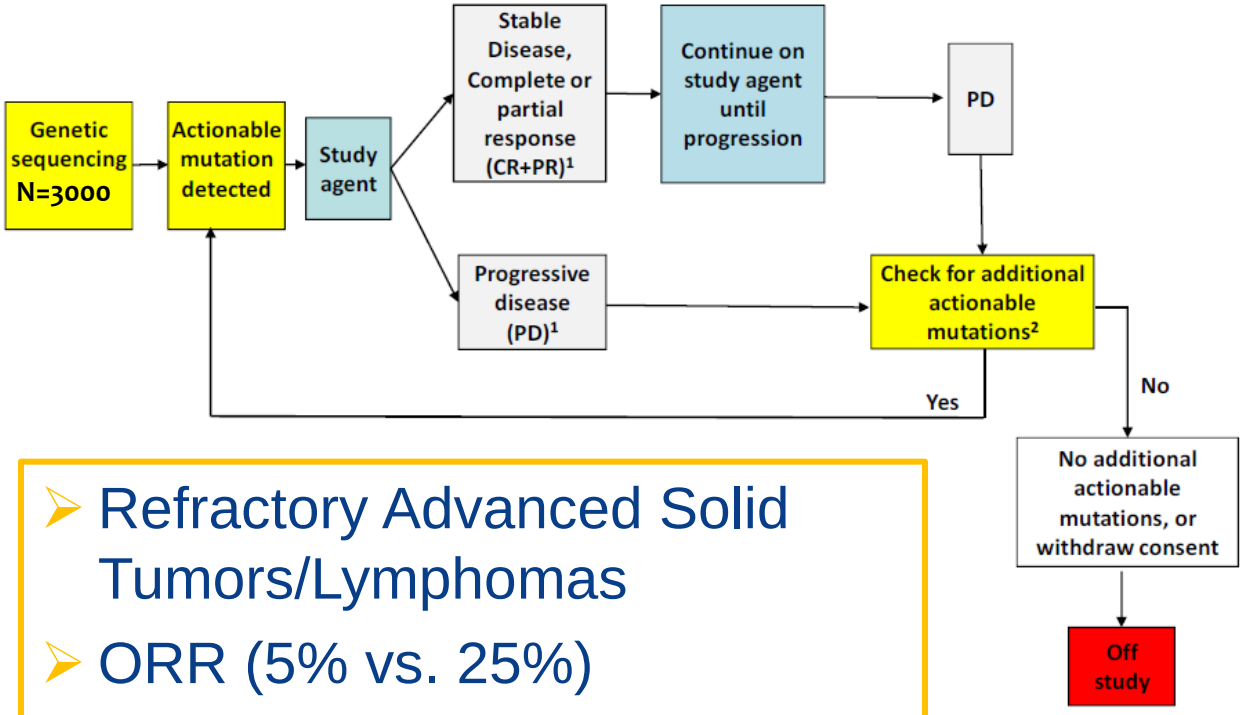
MATCH
(Molecular Analysis for Therapy Choice)



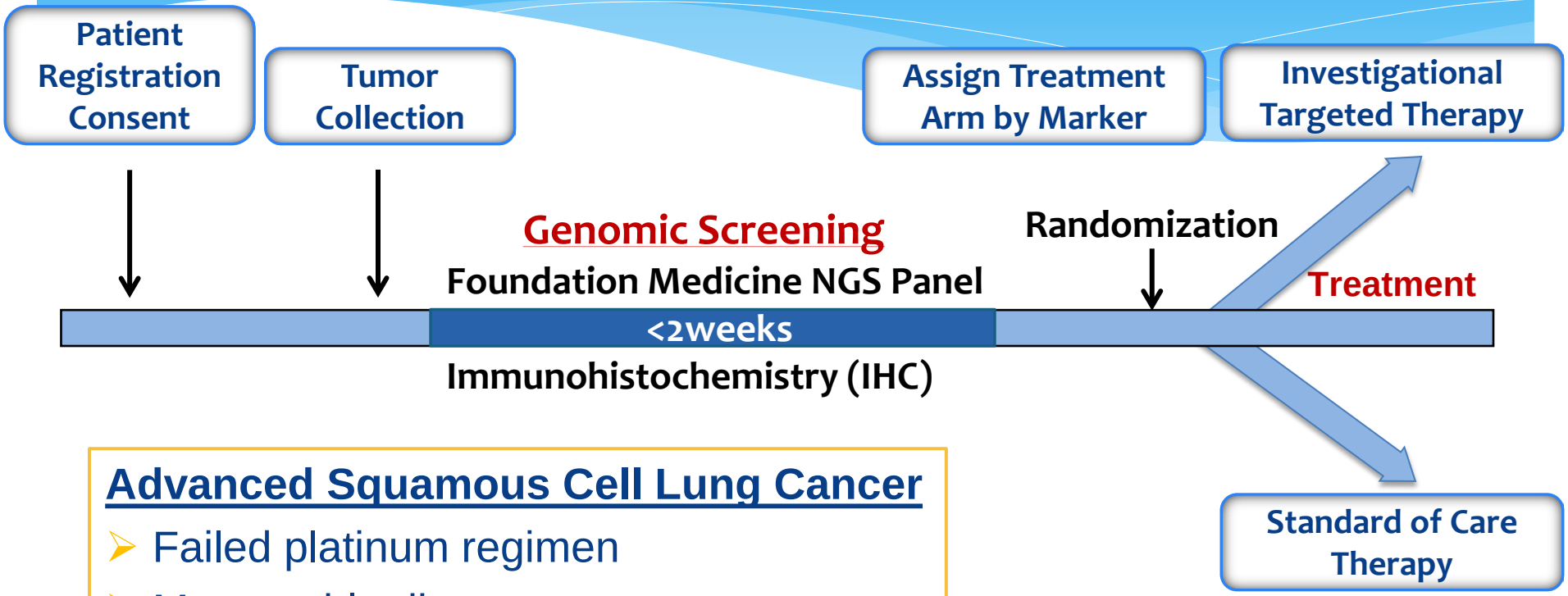
- Refractory Advanced Solid Tumors/Lymphomas
- ORR (5% vs. 25%)
- PFS (6 months: 15% vs. 35%)

- Fresh Bx required
- Network CLIA validated labs
- Targeted NGS
- Non-randomized
- Genes/Drugs selected based on levels of evidence
- 40+ agents pledged with at least RP2D

Umbrella Trials

- Breast (SAFIR-01)
- Colon (FOCUS-4, ASSIGN)
- Melanoma (GEMM)
- Lung (Lung-MAP, BATTLE, MATRIX, SAFIR-02)
- Institution Trials

LUNG-MAP

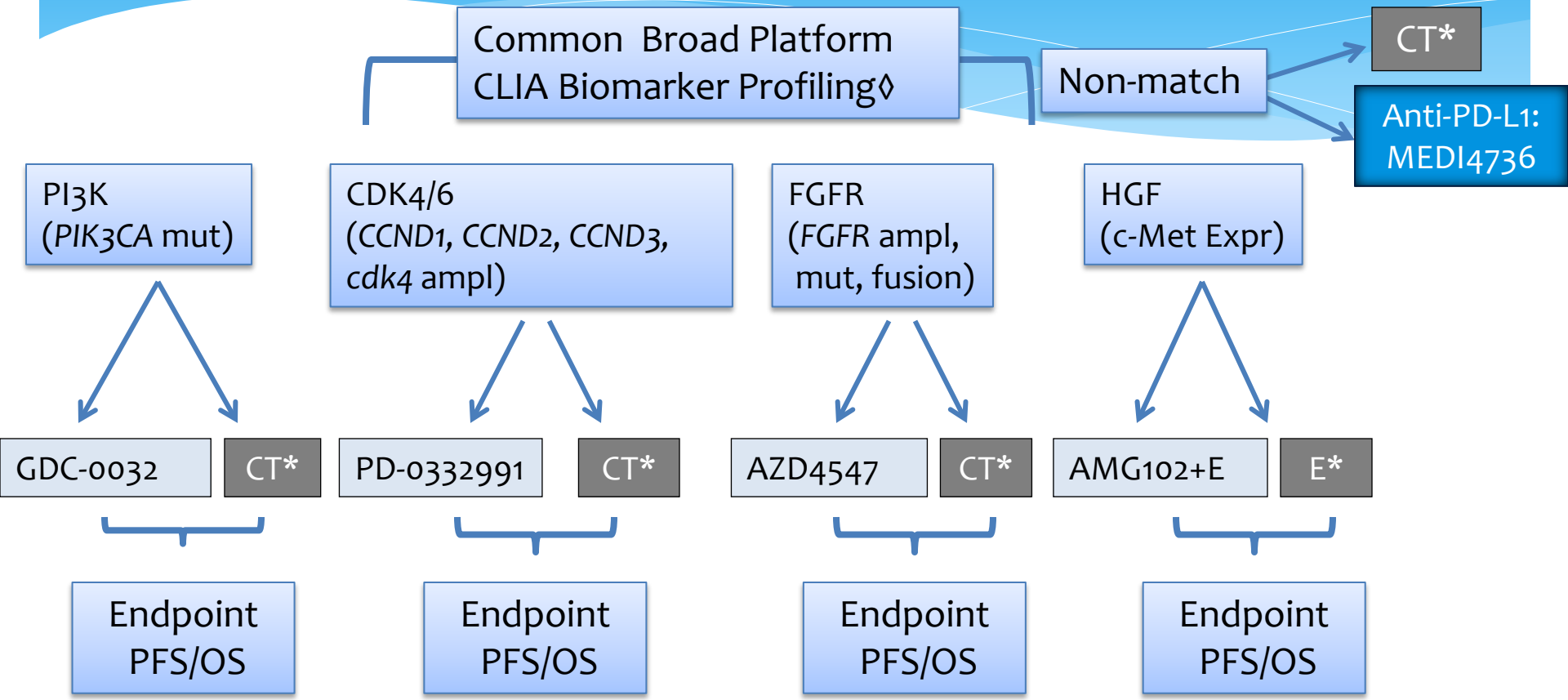


Advanced Squamous Cell Lung Cancer

- Failed platinum regimen
- Measurable disease
- Adequate organ function
- PS 0-1
- Stable or no brain mets

Courtesy of V. Papadimitrakopoulou

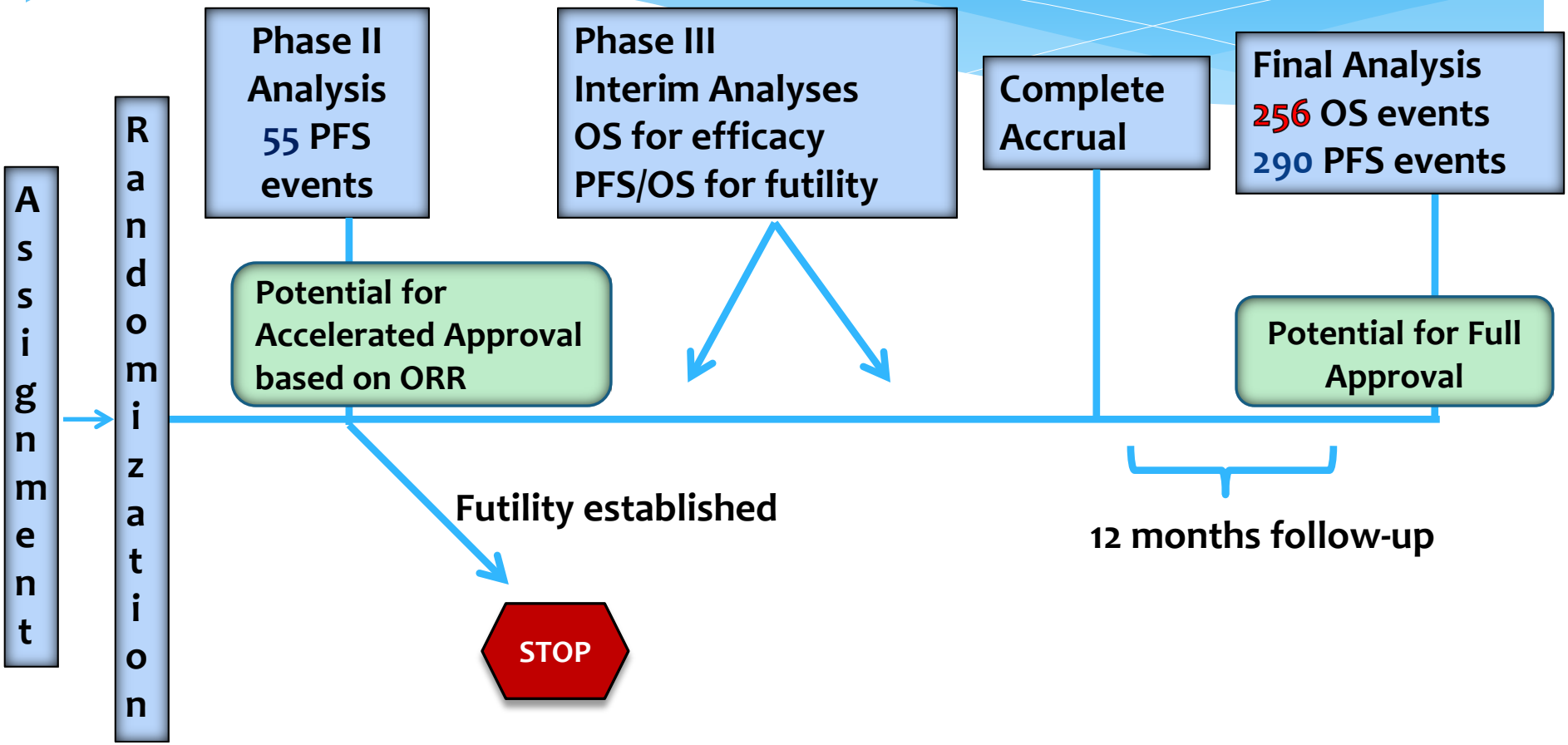
LUNG-MAP



CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib,
◊ Archival FFPE tumor, fresh CNB if needed

Courtesy of V. Papadimitrakopoulou

Study Design Within Each Sub-Study



Courtesy of M. Redman

LUNG-MAP

Sample Size for the Sub-Studies

	Non-match	PI3K	CDK4/6	FGFR	cMET
Prevalence		9%	14%	10%	20%
Assignment Freq.	56%	8%	12%	9%	16%
Phase 2 Size	170	152	124	112	144
Phase 3 Size Analysis	380 21 months	400 72 months	312 45 months	302 53 months	326 37 months
Approx. # needed to screen*	~850	~5,500	~2,700	~3,700	~2,000

*assuming 80% screened will be enrolled

Biomarker-Driven Trial Considerations

- **Genomics**
  - Platform selection
  - Broad vs. targeted screening
  - Central vs. local testing
  - Address heterogeneity
  - Assign therapy
- **Agent Selection**
  - Stage of development
    - Investigational (RP2D?)
    - Approved in other malignancy
  - Single agent or combination
- **Study Design**
  - Fresh biopsy vs. prescreen
  - Outcomes/Endpoints
  - Patient population
  - Non-match arm?
  - Data collection
  - Companion Diagnostic
  - Regulatory Goal

Breast Cancer Trial Considerations and Conclusions

* It is possible to conduct a large genomically-driven trial
* A registration trial is achievable
* Many options for genomics/agent selection and design
* Potential for innovation
* Cooperation between stakeholders
* International trial/global collaboration will expedite accrual

Backup Slides

- Lung-MAP Statistical Design
- GEMM
- MPACT
- BATTLE
- SAFIR-01
- ASSIGN
- FOCUS4
- My Pathway
- Signature Program
- MATRIX
- SAFIR-02

Lung-MAP Statistical Design: Phase II Interim Analysis

	Phase II Design	
	Plan A	**Plan B**
Primary Outcome	**PFS**	
Sample Size	**55 progression events**	
Target HR (% improvement)	**HR = 0.5 2-fold increase**	**HR=0.4 2.5-fold increase**
Power	**90%**	**95%**
Type I error	**10%**	**4%**
Approx. Threshold to continue:		
HR % improvement	**HR= 0.71 41% increase**	**HR = 0.61 63% increase**

Each sub-study can choose between Plan A or Plan B to determine "bar" for continuation past Phase 2 interim analysis

Courtesy of M. Redman

Lung-MAP Statistical Design: Phase III

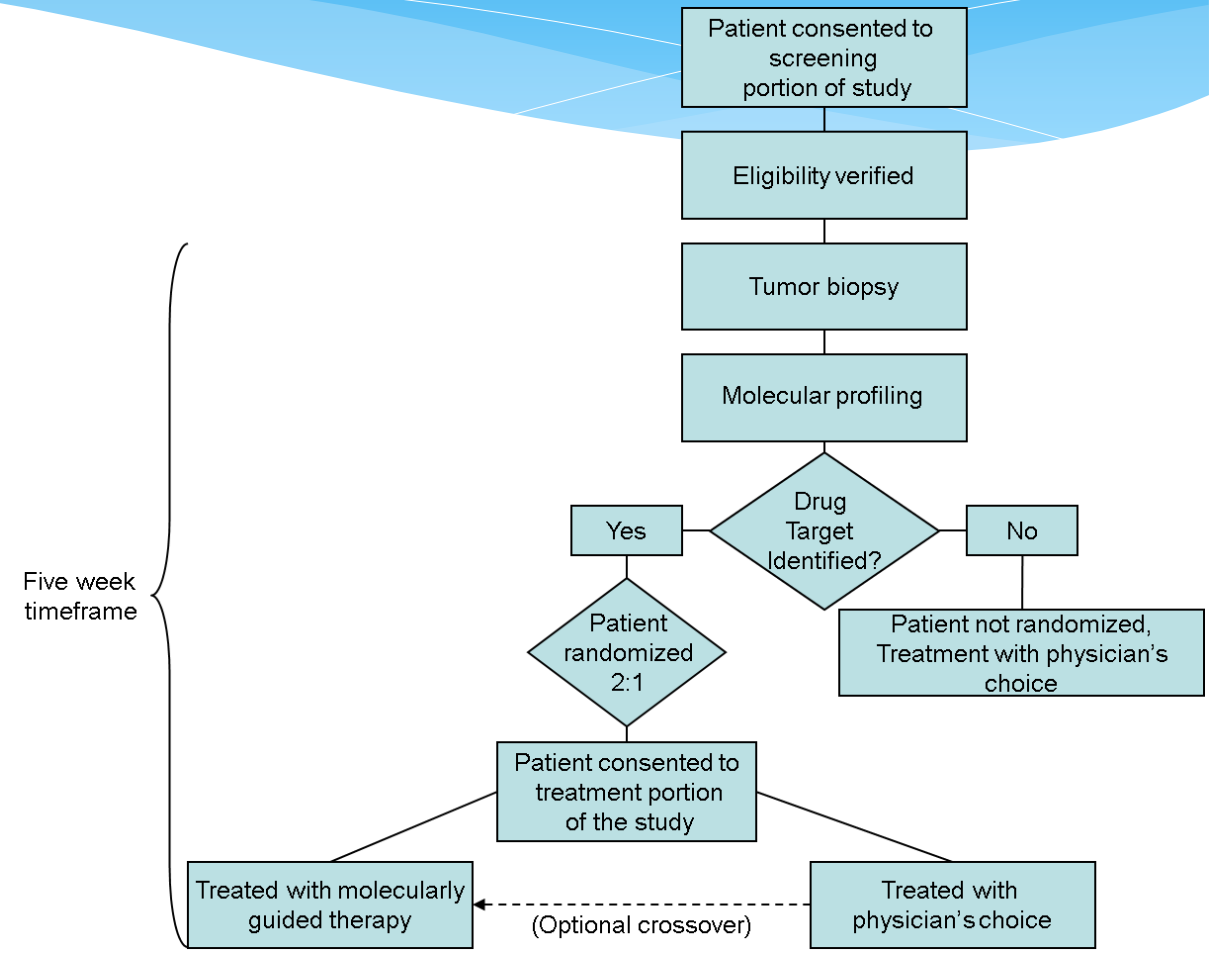
	PFS and OS Co-primary	
	PFS	**OS**
Events	290	256
Null Hypothesis (HR)	0.75* (33% improvement)	1.0 (equivalence)
Alternative Hypothesis	0.5 (2-fold increase)	0.67 (50% improvement)
Type I error (1-sided)	0.014 against HR = 1.33 < 0.00001 against HR = 1	0.025
Power	90%	90%

** Non HR = 1 null hypothesis encodes clinical significance*
Sample size based on OS for all studies

Courtesy of M. Redman

GEMM

- Non-BRAF Mutant Metastatic Melanoma Previously Treated with Immunotherapy
- 136 patients over 18 months for 96 evaluable patients
- Molecular and clinical tumor boards selects therapy



Courtesy of P. LoRusso

Available Commercial Agents for GEMM:

Drug Name:	Target:	Route
Adriamycin	DNA, TOP2A	IV
Bortezomib-TBD	proteasomes	IV
Carboplatin	DNA	IV
Dacarbazine	POLA2	IV
Dasatinib	C-Src	Oral
Erlotinib	EGFR, NR1I2	Oral
Etoposide	topoisomerase-2	IV
Gemcitabine	RRM1, TYMS, CMPK, DNA	IV
Imatinib	Multikinase (BCR-ABL, c-kit, PDGF-R, RET)	Oral
Interferon, Recomb.	IFNAR2, IFNAR1	Sub-Q
Paclitaxel	TUBB1, BCL2	IV
Pemetrexed	TYMS, ATIC, DHFR, GART	IV
Sorafenib	BRAF, RAF1, VEGFR2, VEGFR3, FLT3, PDGFRB, KIT, FLT4	Oral
Temozolomide	DNA	IV
Vorinostat	pan-histone deacetylase inhibitor	Oral
Inlyta (axitinib)	VEGFR	Oral
Bosulif (bosutinib)	Abl, Src	Oral
Sutent (sunitinib)	PDGFRa, PDGFRb, VEGFR1, VEGFR2, VEGFR3, KIT, FLT3, CSF1R, RET	Oral
Torisel (temsirolimus)	FRAP1	IV
Xalkori (crizotinib)	ALK, ROS1, MET	Oral

Courtesy of P. LoRusso

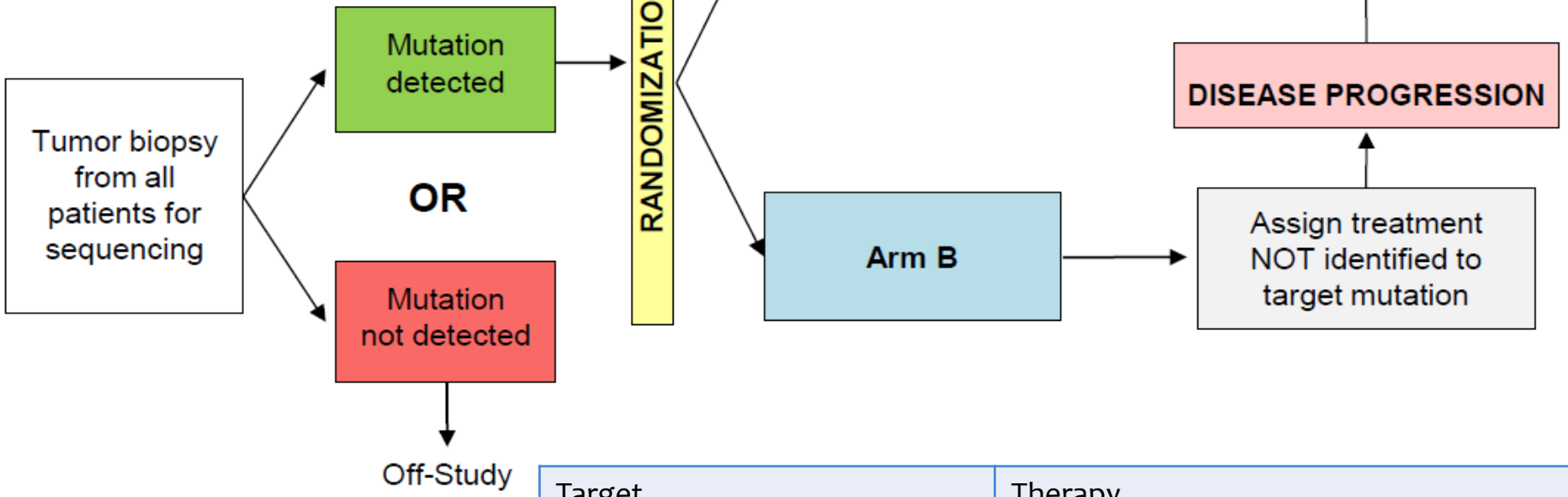
Available Investigational Agents for GEMM:

Company Name:	Drug Name:	Target:	Route
Millennium	MLN8237	Aurora A kinase	Oral
	MLN9708	proteasome protease inhibitor	Oral
Pfizer	PF-00299804	pan-erbB	Oral
	PD-0332991	CDK 4/6 inhibitor	Oral
Plexxikon	PLX3397	FMS, Kit and Fit3-ITD	Oral
Exelixis	XL184	Mulit-kinase (VEGFR2, Met, FLT3, Tie2, Kit and Ret)	Oral
Novartis	MEK162	MEK 1/2	Oral
	BGJ398	FGFR 1/2	Oral
GlaxoSmithKline	GSK1120212 (GSK212)	MEK 1/2 (may be used in combination with GSK795)	Oral
	GSK2141795 (GSK795)	AKT (may be used as monotherapy or in combination with GSK212)	Oral

Courtesy of P. LoRusso

MPACT

- Refractory solid tumors
- Response rate (CR+ PR) and PFS (4 months)

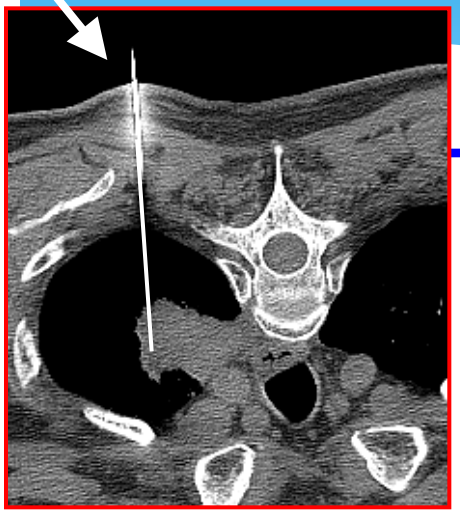


391 mutations, 20 genes, 3 pathways, 4 treatments

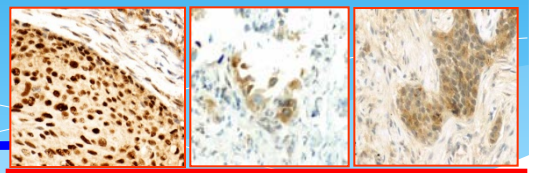
Target	Therapy
DNA repair pathway	**1.** Veliparib (PARPinh) + Temozolomide **2.** MK1775 (WEE1inh) + carboplatin
PI3K pathway, loss of PTEN, Akt Amplification	**3.** Everolimus
RAS pathway	**4.** GSK 1120212 (MEK inhibitor)

BATTLE 1

Umbrella Protocol

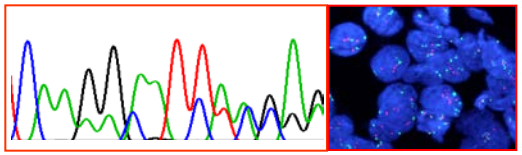


Core Biopsy



Biomarker Profile

EGFR KRAS/BRAF
VEGF RXR/CyclinD1



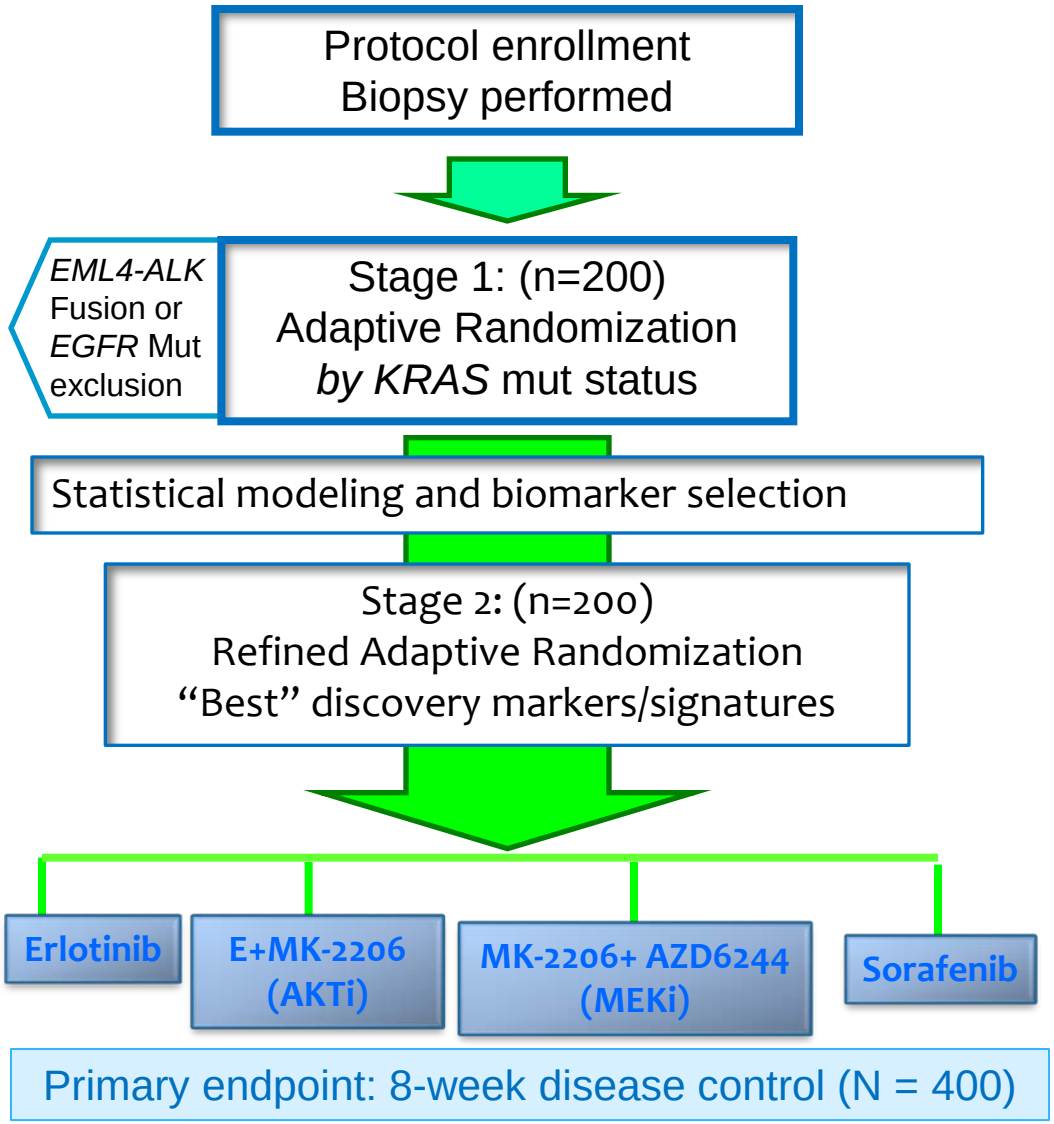
Randomization:
Equal → *Adaptive*

Erlotinib | Vandetanib | Erlotinib + Bexarotene | Sorafenib

Primary end point: 8 week Disease Control (DC)

Courtesy of V. Papadimitrakopoulou
Kim E et al AACR 2010

BATTLE-2

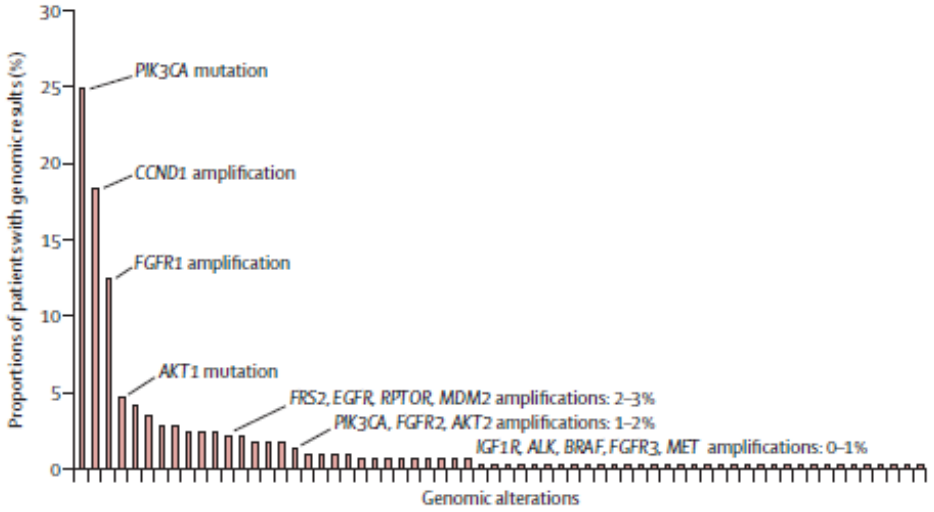


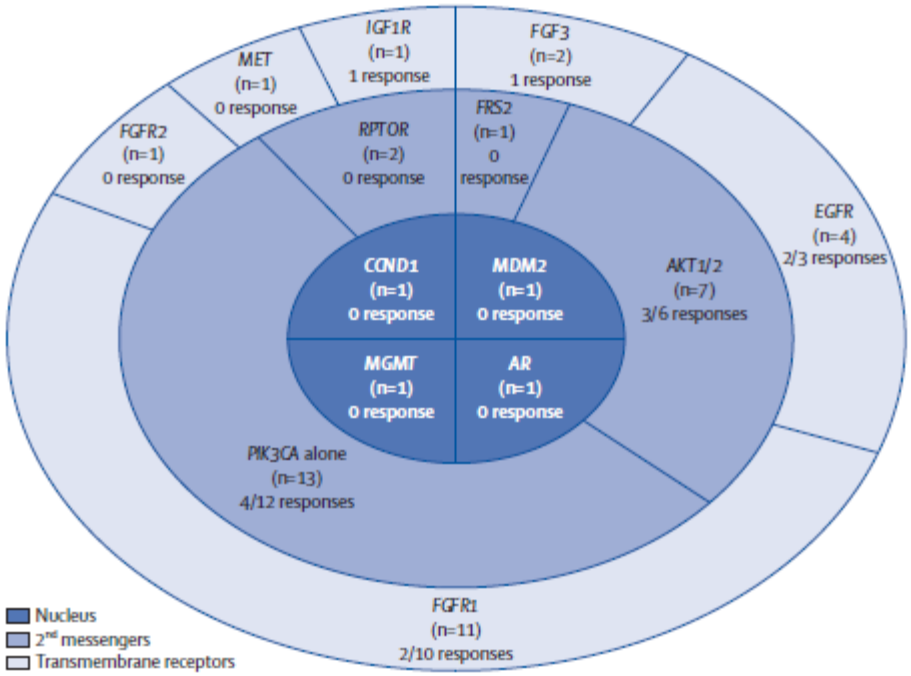
Discovery Markers:

- Protein expression (IHC): ip-AKT (Ser473), PTEN, HIF-1α, LKB1
- Mutation analysis (Sequenom): *PI3KCA*, *BRAF*, *AKT1*, *HRAS*, *NRAS*, *MAP2K1* (*MEK1*), *MET*, *CTNNB1, STK11* (*LKB1*)
- mRNA pathways activation signatures: Affymetrix®
  - BATTLE-1: WT-*EGFR*-Erlotinib, EMT, and Sorafenib
  - BATTLE-2: new "discovery" signatures
- NGS-Foundation Medicine
- RNA sequencing

Courtesy of V. Papadimitrakopoulou

SAFIR-01





423 patients enrolled

16 excluded because no biopsy result

407 with biopsy results

4 excluded because metastatic breast cancer not confirmed

403 biopsy samples assessed

104 excluded
- 91 low percentage of tumour cells
- 8 no frozen material
- 5 other reasons

299 samples with DNA suitable for genomic analysis*
- 2 CGH array alone
- 281 CGH array and Sanger sequencing
- 16 Sanger sequencing alone

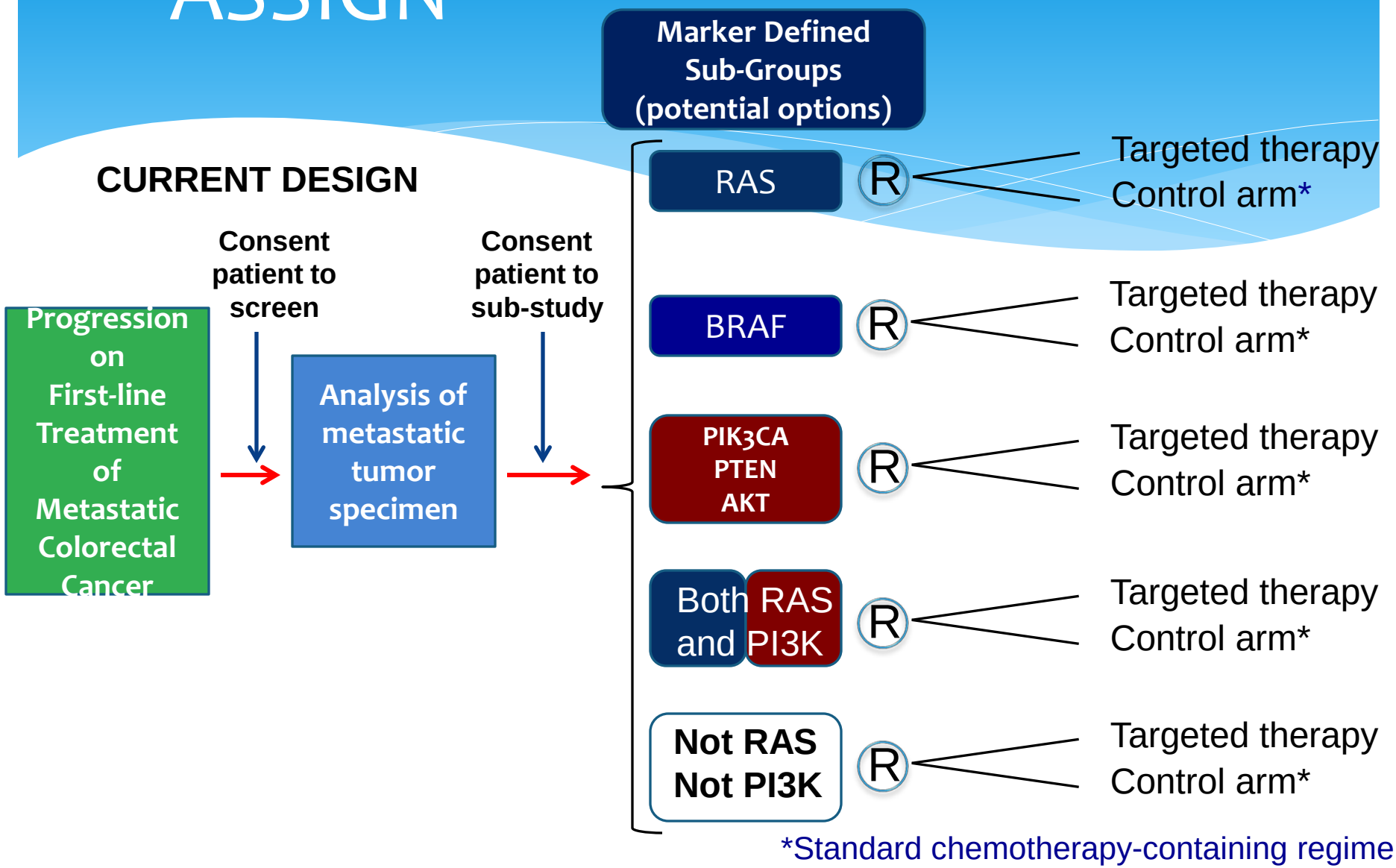
21 excluded
- 16 CGH array results deemed uninterpretable
- 2 not enough DNA for Sanger sequencing

195 patients with targetable genomic alterations

55 patients received matched therapy
- 52 driven by genomics
  - 3 *HER2* amplification on CGH array

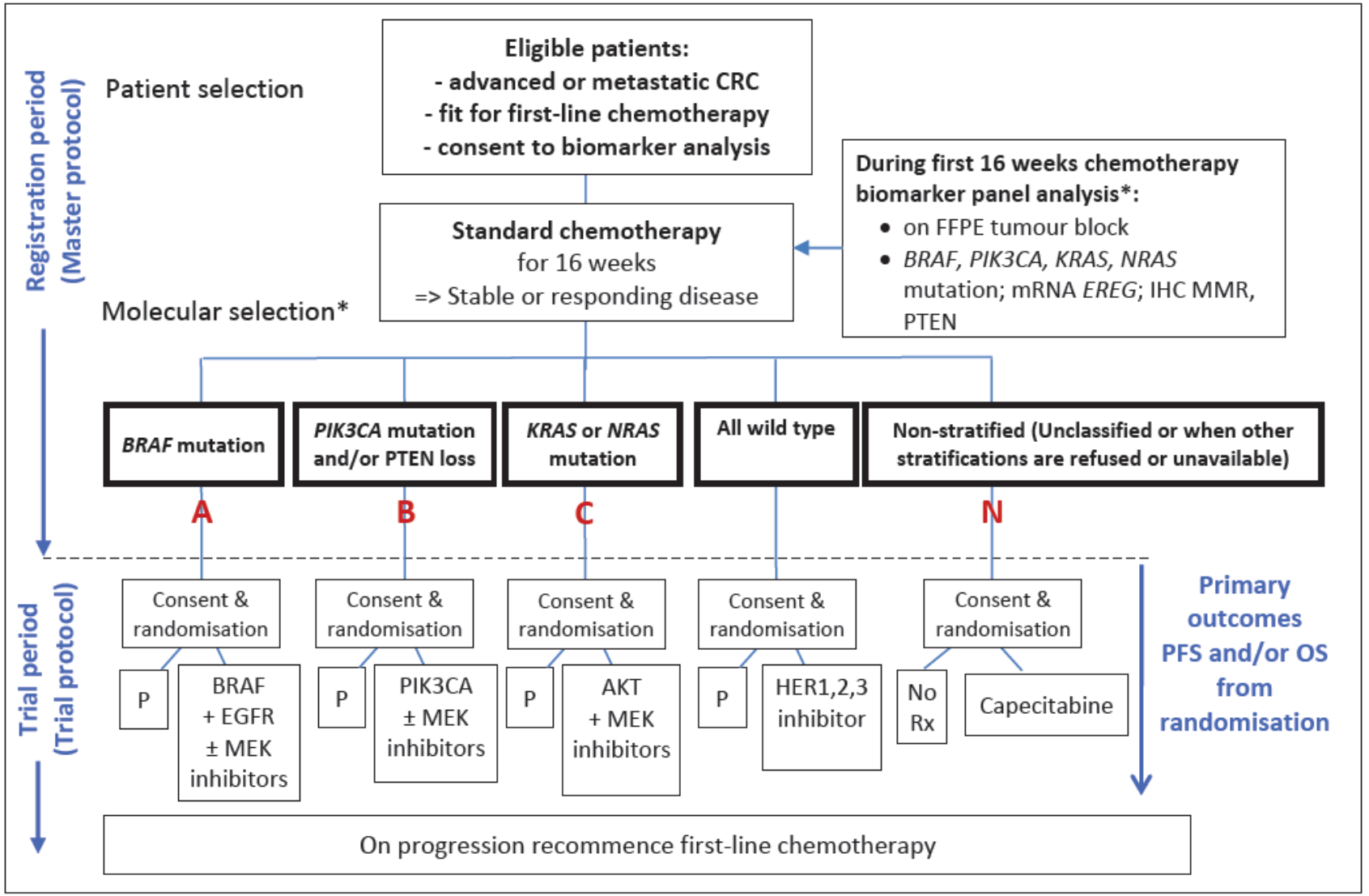
André et al. Lancet Oncology 2014

ASSIGN



Courtesy of P O'Dwyer

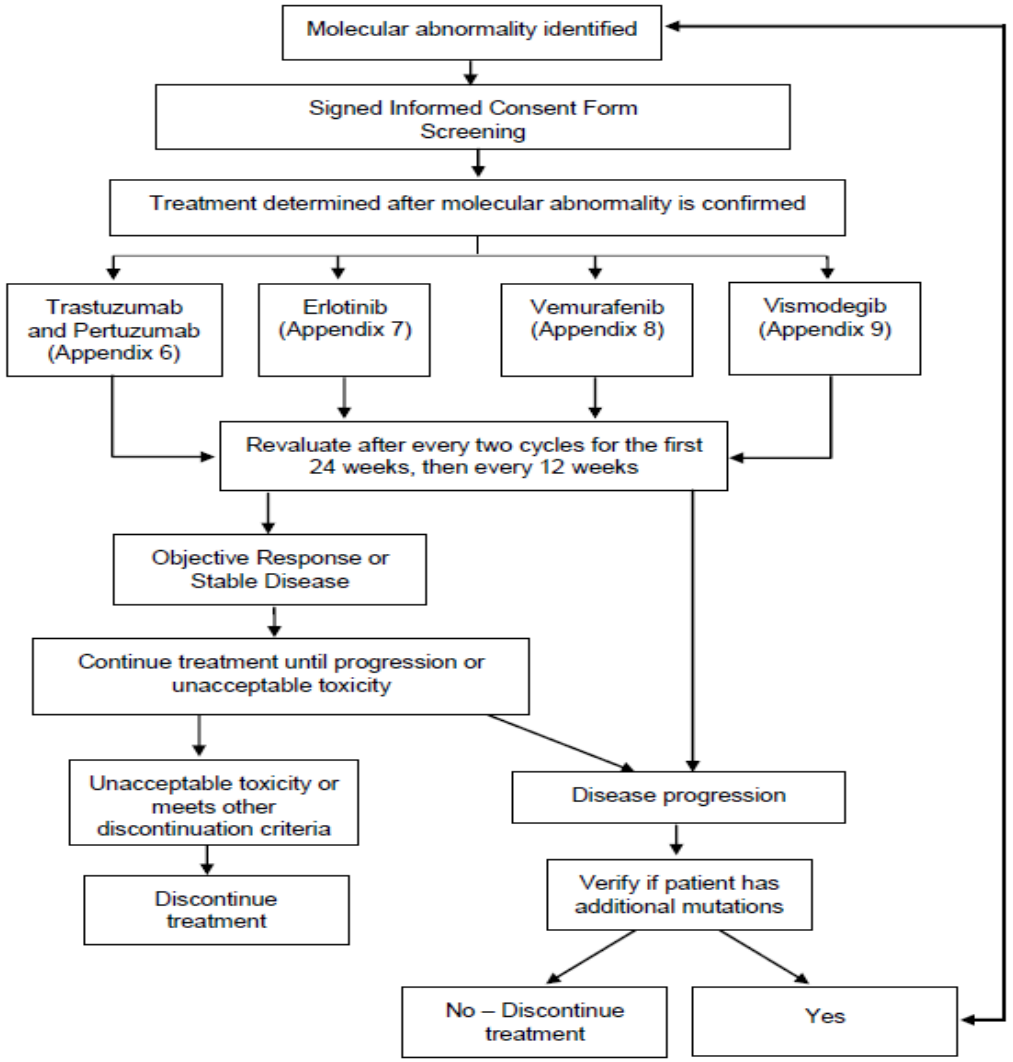
FOCUS4



** The molecular cohorts are arranged in a hierarchy from left to right. For example a patient with both a PIK3CA mutation and a KRAS mutation will be classified into the PIK3CA mutation cohort.*

Genentech My Pathway

Figure 1 Main Study Schema



Courtesy of Genentech

My Pathway Study Schema

Patients with refractory metastatic cancers with locally determined mutations and/or overexpression that are targets for the drugs in this study outside of the approved use

Standard single agent or combination targeted therapy as follows:

- HER2 amplification, overexpression or mutation: trastuzumab and pertuzumab
- EGFR activating mutation: erlotinib
- BRAF mutation (v600e and others): vemurafenib
- Hedgehog pathway activating mutations (Smo/PTCH): vismodegib

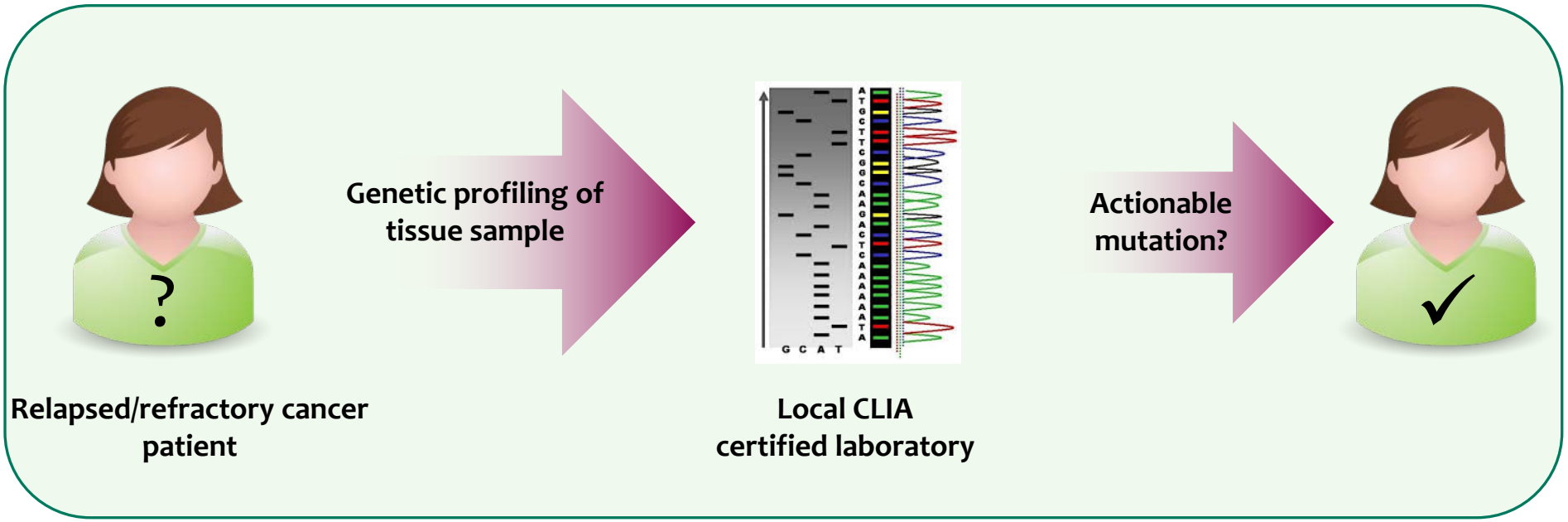
Treat until Investigator determined PD or unacceptable toxicity

Patients with more than one of these abnormalities in their tumor profile will be selected after discussion between the treating physician and the PI based on the mutation considered most critical

Courtesy of Genentech

What Is the Signature Program?

- Background
  - The SIGNATURE program rapidly matches patients to treatments that target their tumor's molecular abnormality and brings the trial to the patient rather than the patient traveling to a clinical trial



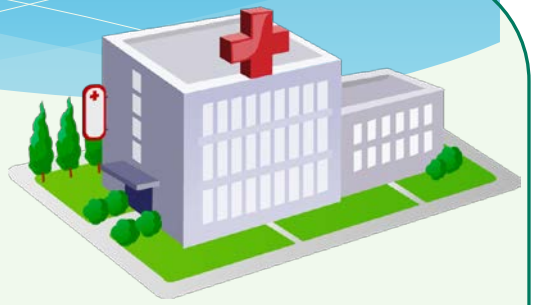
Slosberg E, et al. *J Clin Oncol*. 2014;32(suppl) [abstract TPS2646].
Courtesy of Novartis

How Does the Program Work?

1-855-744-6727

Protocol package

- Fixed contract
- Central institutional review board
- Standard budget
- Standard informed consent



When a patient is identified as having an actionable mutation, their oncologist contacts Novartis

Call center prequalifies the patient:
(1) Protocol package sent to site
Expedited site visit

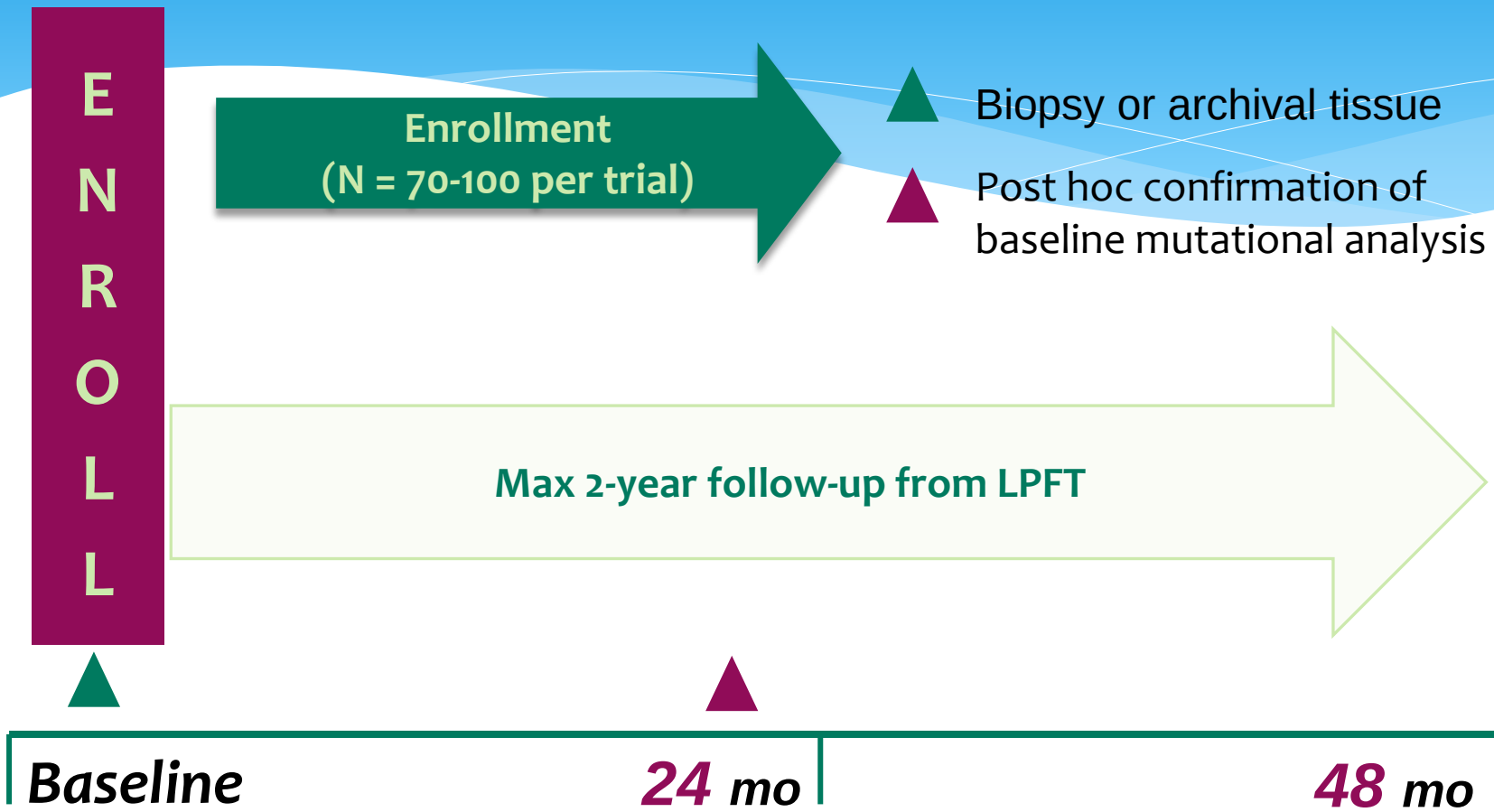
(2)

Study open!

- 5 weeks vs 34-week average

Slosberg E, et al. *J Clin Oncol*. 2014;32(suppl) [abstract TPS2646].
Courtesy of Novartis

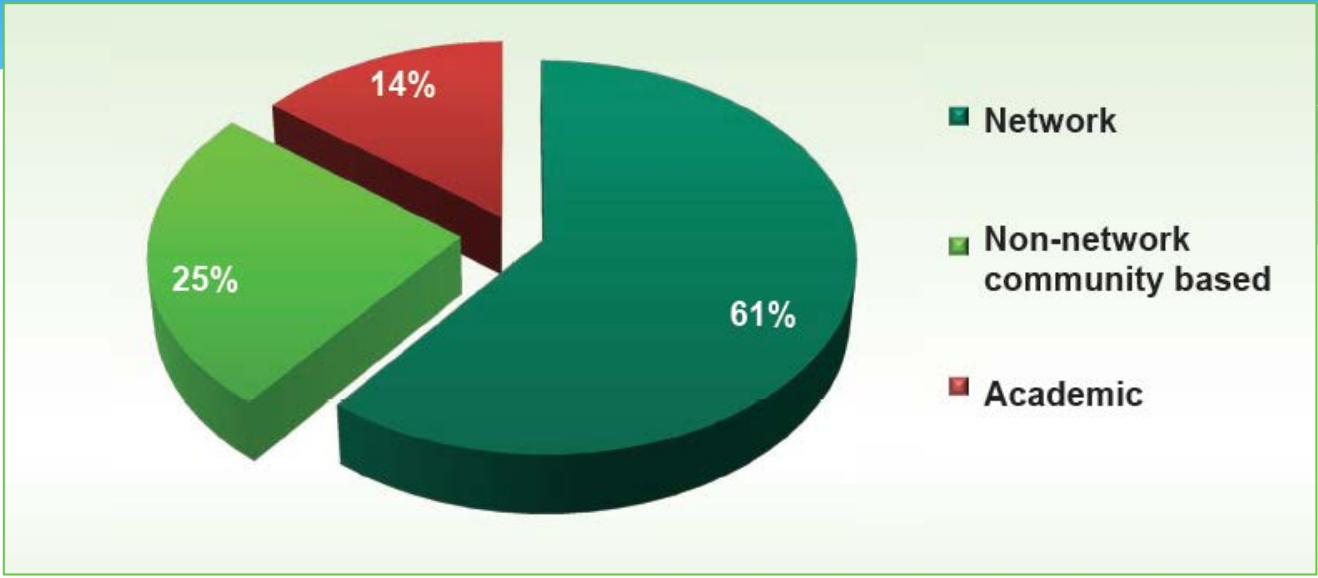
Novartis Signature Study



LPFT, last patient first treatment.

Courtesy of Novartis

Participating Sites (N = 104)



- Any research-experienced site in the US accepting our study model and with a preidentified patient to participate is eligible

Site Type	Number of Sites (N = 104)	Average Weeks to Trial Start	Patients Dosed (N = 121)
Network	63	3	78
Non-network community based	25	6	16
Academic	16	12	27
Average start-up time across 104 sites = 5.2 weeks			

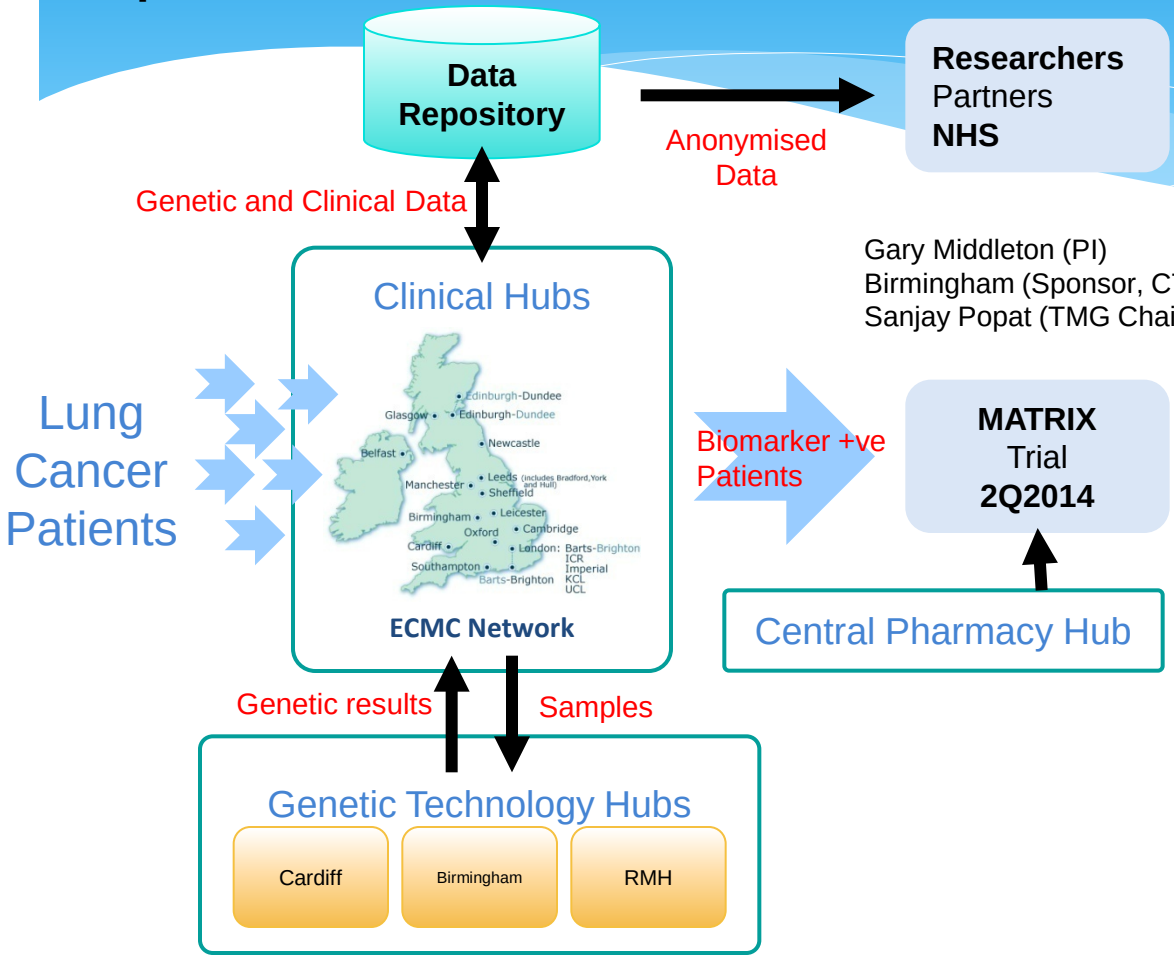
Courtesy of Novartis

Signature- Current Compounds Available

- BKM120 (Pan PI3Ki)
- TK1258 (FGFRi)
- MEK162 (MEKi)
- LGX818 (RAFi)
- LED225(SMOi)
- Additional Agents Planned (LDK378 LEE011, BGJ398 and combinations)

MATRIX National Lung Trial CRUK

Squamous and adenocarcinoma NSCLC



Gary Middleton (PI)
Birmingham (Sponsor, CTU)
Sanjay Popat (TMG Chair)

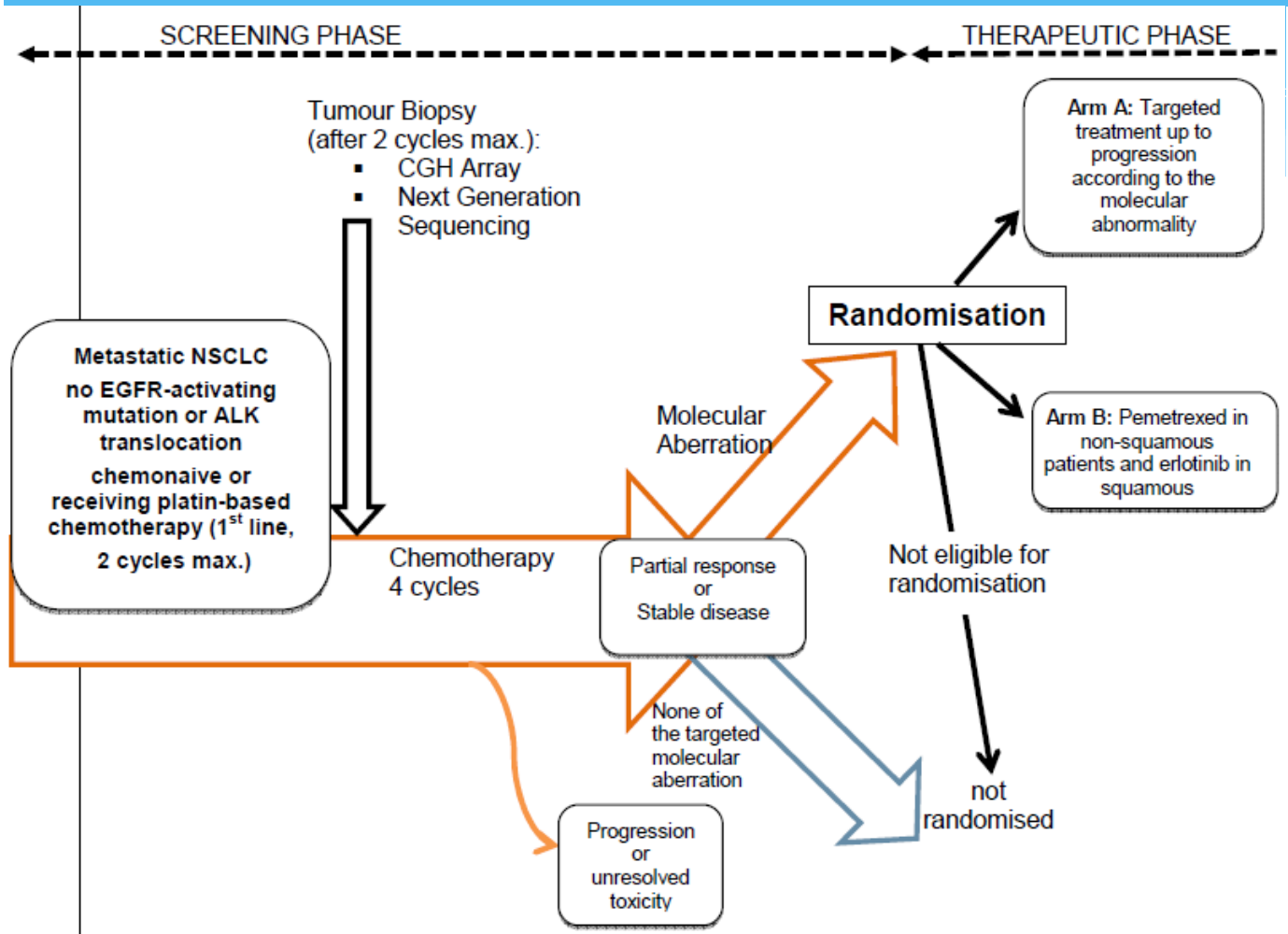
CANCER RESEARCH UK

Compound	Molecular segment	Prevalence
AZD5363	PI3KCA mutation PIK3CA mutation AKT1 mutation PIK3CA amp PTEN null	4.6% 15.2% 0.9% 7.0% 7.9%
AZD4547	FGFR2/3 mutation FGFR2/3 mutation	3.3% 4.4%
AZD2014	LKB1 mutation TSC1/2 mutation	12.2% 8.9%
AZD9291	T790M (Her2 amp)	7.5% (5.0%)
Selumetinib/ docetaxel	KRAS wild type, NF1, NRAS, HRAS mutation	24.9%
MEDI4736	All markers negative (PD-L1 positive)	est. 40%

Courtesy of A. Hughes (presented at ESMO 2014)

SAFIR02 Lung Trial – UNICANCER

Squamous and adenocarcinoma NSCLC



Compound	Molecular segment
AZD5363	PI3KCA mutation AKT1 mutation PIK3CA amp PTEN loss PTEN mutation
AZD4547	FGFR1 amplification
AZD2014	LKB1 mutation
AZD8931	HER2 mutation HER2 amplification
Selumetinib	KRAS mutation BRAF mutation
Vandetanib	RET mutation

Courtesy of A. Hughes (presented at ESMO 2014)